

## Long-term outcomes following “presumed” total parathyroidectomy for secondary hyperparathyroidism of chronic kidney disease

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**SUMMARY:** Long-term outcomes following “presumed” total parathyroidectomy for secondary hyperparathyroidism of chronic kidney disease.

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*Aim.* The most efficacious surgical treatment for renal hyperparathyroidism is still subject of research. Considering its low incidence rate of long-term relapse, “presumed” total parathyroidectomy without autotransplantation (TP) may be indicated for secondary hyperparathyroidism (2HPT) in patients with chronic kidney disease (CKD), not eligible for kidney transplantation. The aim of this study was to analyse the TP long-term results in 2HPT haemodialysis (HD) patients.

*Method.* Between January 2004 and October 2009, 25 2HPT HD patients, not eligible for kidney transplantation, underwent TP of at least four parathyroid glands. Clinical status and intact parathyroid

hormone (iPTH) serum levels were assessed intraoperatively and during a 36-month follow-up.

*Results.* TP improved the typical clinical symptoms and a significant reduction of iPTH serum levels was achieved in each patient. Aparathyroidism was never observed; in case of severe postoperative hypocalcemia, hypocalcemic seizures were never reported and the long-term recurrence rate was 8%. Only one patient received a kidney transplantation. Postoperative cardiovascular events (hypertension, peripheral artery disease, arrhythmia, coronary or cerebrovascular disease) were observed in 32% of cases and mortality rate was 16%.

*Conclusions.* Considering its low long-term relapse rate and the absence of postoperative aparathyroidism, TP may still be considered the treatment of choice in patients with aggressive forms of 2HPT or of advanced dialytic vintage, with no access to renal transplantation. In case of postoperative hypoparathyroidism, hypocalcaemia can be effectively managed by medical treatment.

KEY WORDS: Total parathyroidectomy - Secondary hyperparathyroidism - Haemodialysis - Aparathyroidism.

### Introduction

In haemodialysis (HD) patients affected by chronic kidney disease (CKD), the risk of secondary hyperparathyroidism (2HPT) rises along with dialytic vintage, inducing a higher mortality rate particularly due to irreversible cardiovascular complications. Before the calcimimetics era, parathyroidectomy (PTx) was required in 2.5% of dialysis patients for year (1). Considering its association with the postoperative severe hypocalcaemia, and the potential onset of “adynamic” bone disease following surgery, total parathyroidectomy without autotransplantation (TP) was in the past reserved only to selected patients affected by severe 2

HPT of CKD. On the contrary, more recent literature data demonstrated that TP is a safe procedure, that the dreaded postoperative aparathyroidism is very rare, that hypoparathyroidism and hypocalcaemia can be effectively treated by the proper drugs with a low long-term recurrence rate reported (2-5). In the present series, we analysed the clinical/laboratory long-term results of patients affected by 2HPT of CKD not eligible for kidney transplantation, undergoing TP in Southern Italy. The unsystematic removal of at least 4 parathyroid glands was considered a criterion of exclusion from the study.

### Patients and methods

Data were retrospectively collected from 25 consecutive patients (8 and 17 ), affected by severe 2HPT of CKD resistant to medical treatment, on standard three times weekly HD, not eligible for kidney transplantation, observed between January 2004 and October 2009. All patients, addressed to our Institution from regional HD centres, gave their informed consent to be enrolled in the study.

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The mean age was 58 years (range 26-72), with a mean dialytic vintage of 12 years (4-28 years). 10 patients (40%) suffered from co-existing thyroid disease. Diffuse itching, arthromyalgia and mood alterations (changes in emotional state, sleep disorders, apathy, reduced social-environmental interactions) were reported in every case, while cardiovascular disorders (hypertension, previous myocardial infarction, etc.) was found in 60%. There were no cases of calcium therapy. Indications to the surgical procedure were set down according to both K/DOQI 2003 guidelines and Tominaga (6,7). Preoperative diagnostic work-up consisted of: high-resolution neck ultrasonography, associated to fine needle biopsy of thyroid nodules; ENT examination; technetium- 99m-sestamibi scintigraphy of neck and mediastinum; echocardiography; computed bone mineralometry. All blood samples were withdrawn before dialysis to minimize the dilution effect on laboratory assays. Intact parathyroid hormone (iPTH), serum calcium (Ca), serum phosphate (P), alkaline phosphatase (ALP), FT<sub>3</sub>, FT<sub>4</sub>, TSH, and thyroglobulin were evaluated. Mean preoperative iPTH was 1541 ng/L, with a range of 400-3100 ng/L, while mean Ca levels were 2.55 mmol/L with a range of 1.87-3.32 mmol/L, and mean P levels were 5.20 mmol/L (Table 1). At least 4 parathyroid glands were removed in all patients (in every case confirmed by intraoperative pathologic examination). Thyrothymic ligament and bilateral thymic tongues were removed in all cases, and exploration of the jugular/carotid axis was performed in order to rule out the presence of ectopic and supernumerary glands. In 10 out of 25 patients (40%) with thyroid gland disease, 8 total thyroidectomies and 2 hemithyroidectomies were performed. Chemiluminescence immunoassay (CLIA), was employed for the quantitative determination of the iPTH (Coefficient of variation: CV% intra assay 1.7-3.7; CV% inter assay 2.6-5.9; limit of detection 0.07 pmol/L). A 10-65 ng/L range was taken as a reference of normal iPTH levels, according to which eu- (10-65), hypo- (< 10 ng/L), aparathyroidism (0 pg/ml), and persistence or relapse (> 65) of the disease were determined. Hypocalcaemia was considered to be present when serum calcium was < 1.97 mmol/L (normal value= 2.1-2.55 mmol/L). Surgical treatment was considered successful in patients with a postoperative iPTH level < 250.2 ng/L. In addition to the intraoperative evaluation, iPTH and calcium were dosed the day after surgery and during a 36-month follow-up. Only in few cases, a HD treatment was required immediately after surgery, because of electrolyte imbalance. Most of patients required intravenous administration of calcium. Only one patient of the present series received kidney transplantation.

## Results

The preoperative diagnostic work-up did not identify supernumerary glands in any patient. TP produced a rapid improvement in osteoarticular symptoms, an increase in muscular strength, and a substantial improvement in mood patterns first, and later in sleep disorders, which were associated to a statistically significant reduction in the requirement of erythropoiesis-stimulating agent (ESA) and to an improvement of Hb levels, as well as of the general quality of life (8-11). After a 36-month follow-up, in each case a clear regression of osteodystrophy was observed, with no reports of delayed pathological fractures. After surgery, all patients reported a dramatic reduction in iPTH levels, both immediately and after three years. Aparathyroidism was

TABLE 1 - PREOPERATIVE DATA.

Pz	Ca	iPTH	P	Ca x P	AP
1	1.87	1425	1.80	3.36	185
2	2.87	1845	2.29	6.57	220
3	2.17	1850	2.74	5.94	559
4	2.92	1585	2.74	8.0	4386
5	2.55	2890	1.03	2.62	158
6	3.32	945	1.38	4.58	520
7	2.82	2496	2.29	6.45	458
8	2.32	874	1.32	3.06	210
9	2.4	3100	2.29	5.49	130
10	2.25	976	1.61	3.62	210
11	2.57	400	1.48	3.80	323
12	2.35	1650	1.29	3.03	998
13	2.3	1570	2.55	5.86	139
14	2.75	790	2.29	6.29	145
15	2.57	2100	2.32	5.96	157
16	2.55	1200	1.32	3.36	250
17	2.1	1490	2.48	5.20	185
18	2.5	1173	1.03	2.57	150
19	2.82	1097	2.71	7.64	267
20	3.02	1365	2.39	7.21	160
21	2.0	430	1.25	2.5	510
22	2.55	2900	2.58	6.57	140
23	3.25	1400	1.80	5.85	830
24	2.25	630	2.71	6.09	190
25	2.37	2350	1.61	3.81	568

Ca= Calcium (n.v. = 2.1-2.55 mmol/L)

P= Phosphate (n.v. = 0.87-1.45 mmol/L)

iPTH= Intact Parathyroid Hormone (n.v. = 10-65 ng/L)

AP= Alkaline Phosphatase (n.v. = 53-128 U/L – Babson units).

never observed after long-term follow-up. Postoperative hypocalcaemia was detected in most patients and was easily corrected by the intravenous administration of calcium. In only one case, Ca level was below 1.5 mmol/L. However, hypocalcemic seizures were never observed. Immediate and long-term results are reported in table 2. The iPTH levels assessed one year after surgery showed euparathyroidism in 52 % of cases (13/25 pts) and a relapse rate of 4 %, which was 8 % (2/25 pts) after 36 months (Table 2). In these patients dialysis vintage was longer than 90 months, and preoperative iPTH levels were > 1400 ng/L. In each patient, the definitive pathologic examination showed hyperplasia of each removed gland; in 2 cases (8%), 5 hyperplastic glands were removed; 8 patients (32%) presented an associated multinodular goiter, 1 (4%) an adenomatous goiter, and 1 (4%) a “small papillary cancer”. In one case,

TABLE 2 - POSTOPERATIVE AND LONG-TERM RESULTS (I POSTOPERATIVE, 1 YEAR AND 3 YEARS AFTER SURGERY).

	Eupara (%)	Hypopara (%)	Persistence (%)	Relapse (%)
I p.o.	56	24	20	-
1 year	52	24	20	4
3 years	52	20	20	8

Ca= Calcium (n.v.= 2.1-2.55 mmoli/L)

P= Phosphate (n.v.= 0.87-1.45 mmoli/L)

iPTH= Intact Parathyroid Hormone (n.v.= 10-65 ng/L)

AP= Alkaline Phosphatase (n.v.= 53-128 U/L – Babson units).

a tracheotomy was required for a late respiratory distress due to a bilateral vocal chords paresis (p.o. III). The cannula was removed after three months, with no phonation impairment. No other significant postoperative complications were observed. In 8/25 patients (32%), postoperative cardiovascular events (hypertension, peripheral arteries disorders, arrhythmia, coronary or cerebrovascular disorders) were observed, and mortality rate was 16 %. One patient died following the rupture of an aneurysm of abdominal aorta, 1 for congestive heart failure and 1 for myocardial infarction. One patient also died for pulmonary cancer. Our data have to increase to obtain more significant data.

## Discussion and conclusions

In our series, analysis of long-term surgical results demonstrates that TP may be considered a safe operation, when treating severe 2 HPT in HD patients unresponsive to medical therapy. It is also properly indicated in aggressive forms of 2HPT or in patients with advanced dialytic vintage, without access to renal transplantation; also it's important to consider the possible arising of parathyroid carcinoma in patients on long-term hemodialysis (12). A fearful postoperative aparathyroidism is very rare, while hypocalcaemia and hypoparathyroidism can be effectively managed by medical treatment. 2HPT has negative effects on patient's quality of life, increasing mortality rate particularly by irreversible cardiovascular complications, as demonstrated in our series. Pathological modifications of mineral metabolism, phosphates over all, worsening atherosclerosis symptoms and favoring arterial stiffness, increase the risk of cardiovascular morbidity and mortality. Therefore, in patients unresponsive to medical treatment, early surgery could offer an improved quality of life and possibly a higher long-term survival rate. Dramatic reduction of iPTH serum levels, reduction in the normal range of Ca, P, Ca x P, increase of haema-

tocrit and of Hb levels and, probably, a significant decrease of ESA requirement, in most operated patients, could explain the beneficial effects of parathyroidectomy on the HD population. Different studies showed that PTx could also improve mortality and cardiovascular morbidity (13,14). The recent diffusion of calcimimetics, to be used in the early stages of the disease, acting on the Ca sensing receptors of the primary cells of parathyroid glands, inhibiting glandular hyperplasia, and reducing significantly the circulating PTH levels (15), will certainly have a major impact on the 2HPT management. In fact, its wide diffusion has reduced the number of patients unresponsive to medical treatment to address to surgery. The removal of at least 4 glands provides excellent results in terms of clinical and laboratory parameters (3,5). Nevertheless, the presence of supernumerary glands (10% of HD population) could negatively influence the results of neck surgery. At present, the rapid intraoperative assay of iPTH allows a substantial improvement in the diagnostic accuracy, and we strongly suggest that it should be considered as a procedure of choice (16,17). In patients awaiting transplant, subtotal parathyroidectomy and TP plus muscular or subcutaneous autotransplantation are the most popular procedures. Nevertheless, they are characterized by a long-term risk of relapse (10% of cases), leading to a higher morbidity, since long afterwards it requires further diagnostic and therapeutic interventions (surgery, percutaneous alcoholisation) (18). KDOQI guidelines confirm the efficacy of different operations, indicating that the selection criteria of the procedure of choice depend on preference and experience of each surgeon (6). Nevertheless, as demonstrated in our series after a long-term follow-up, aparathyroidism following TP seems to be a "virtual" result, and also H. Dralle states that in 2HPT it is extremely difficult to completely abolish parathyroid function (19). The rate of relapse, reported analyzing 147 patients, who underwent TP between 1989 and 2006, varied between 8 and 35% (20). Analysis of our results confirms that TP is a safe procedure, allowing a high postoperative success rate also in patients with a more advanced dialytic vintage and a more aggressive 2HPT. Long-term relapse rate was low (8%), and although a high incidence of hypoparathyroidism was observed, none of patients showed aparathyroidism or hypocalcemic seizures.

In conclusion, in 2HPT patients unresponsive to medical treatment, an early surgical treatment must be considered to reduce the morbidity related to cardiovascular complications. TP without auto transplantation may still be the intervention of choice in patients with aggressive forms of 2HPT or of advanced dialytic vintage without possibility of renal transplant. Long-term aparathyroidism is very rare, and a low rate of long-term relapse is reported.

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